REMARKS

Claims 1-14, and 16-21 are pending in the application. Claims 16-21 have been withdrawn from consideration as directed to non-elected inventions. Claims 1-14 have been rejected.

Claims 1, 7-10, 14, 16, and 19 have been amended. Rejoinder of Claims 16-21 and reconsideration and allowance of Claims 1-14 and 16-21 in view of the above amendments and following remarks is respectfully requested.

The Rejection of Claims 8 and 10 Under 35 U.S.C.§112, First Paragraph

Claims 8 and 10 have been rejected under 35 U.S.C. §112, first paragraph, as failing to meet the written description and enablement requirements.

The Examiner has indicated that the term "derivatives" is not supported by the specification. Applicants have amended Claims 8, 10, and withdrawn Claim 16 to delete the term. In view of the amendment of Claims 8 and 10, withdrawal of the rejection is requested.

The Rejection of Claims 1 and 9 Under 35 U.S.C.§112, First Paragraph

Claims 1 and 9 have been rejected under 35 U.S.C. §112, first paragraph, as failing to meet the written description requirement.

The Office Action indicates that the phrase "substantially pure" in Claim 1 is not supported by the specification. Applicants have amended Claim 1 by deleting the phrase. In view of the amendment of Claim 1, withdrawal of the rejection is requested.

The Office Action indicates that the disclosure provides no discussion of the point of comparison for the increase in nanocrystalline and amorphous drug present in the product due to the practice of the claimed process. Claim 9 depends from Claim 1 and recites that the drug loaded in the cross-linked polymer has increased amorphous and nanocrystalline fraction compared to the original drug that is dissolved in the supercritical fluid. Applicants refer the

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Examiner to paragraph [0024] of the published application where it is stated that the claimed method provides that the drug incorporated in the polymer shows an increased amount of its highly bioavailable amorphous and nanocrystalline fractions. Applicants submit that the specification makes clear that the increase for the incorporated drug is relative to its original form. Withdrawal of the rejection is requested.

The Rejection of Claim 9 Under 35 U.S.C.§112, First Paragraph

Claim 9 has been rejected under 35 U.S.C. §112, first paragraph, as failing to meet the enablement requirement.

Claim 9 depends from Claim 1 and recites that the drug loaded in the cross-linked polymer has increased amorphous and nanocrystalline fraction compared to the original drug that is dissolved in the supercritical fluid. The Office Action states that, although Claim 9 is enabled for the process in which the loaded drug is in an amorphous form in a larger proportion than before it was loaded into the polymer, there is no enablement for the process where the drug is loaded in amorphous and nanocrystalline form.

Applicants have amended Claim 9 by deleting the phrase "and nanocrystalline form." As amended, Claim 9 recites that the drug loaded in the cross-linked polymer has increased amorphous fraction compared to the drug dissolved in the supercritical fluid. In view of the amendment of Claim 9, withdrawal of the rejection is requested.

The Rejection of Claims 1, 8, and 10 Under 35 U.S.C.§112, Second Paragraph

Claims 1, 8, and 10 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite.

The term "substantially" in Claim 1 is considered to be indefinite. Claim 1 has been amended to delete the phrase "substantially pure." In view of the amendment of Claim 1, withdrawal of the rejection is requested.

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The term "cross-linked" in Claims 8 and 10 is considered to be inaccurate with regard to cyclodextrin. Claims 8 and 10 have been amended to recite "cross-linked cyclodextrin." Support for the amendment can be found throughout the specification as originally filed. See, for example, paragraph [0019] of the published application ("[c]ross-linked polymers useful for the present invention are any polymers . . . whose polymeric chains are cross-linked by interchain bonds . . . [which] can be added by performing ad-hoc cross-linking reactions." In view of the amendment of Claims 8 and 10, withdrawal of the rejection is requested.

The Rejection of Claims 1-9 Under 35 U.S.C.§103(a)

Claims 1-9 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,670,454, issued to Lai et al., in view of WO 99/25322, Carli et al. Withdrawal of the rejection is requested for the following reasons.

As amended, Claim 1 is directed to a process for loading a drug into a cross-linked polymer that includes the steps of (a) pre-treating a cross-linked polymer with supercritical fluid free from any drugs, (b) contacting the pre-treated cross-linked polymer with a supercritical fluid containing a dissolved drug, and (c) removing the supercritical fluid, thereby causing the drug to precipitate inside the cross-linked polymer. Claims 2-9 depend from Claim 1.

Support for the amendment to Claim 1 can be found throughout the specification as originally filed. For example, see paragraph [0013] of the published application.

The cited references fail to teach every element of the claimed invention

The cited references fail to teach or suggest any method for loading a drug into a cross-linked polymer that includes the step of pre-treating the cross-linked polymer with supercritical fluid free from any drug prior to subsequently contacting the pre-treated cross-linked polymer with supercritical fluid that does include a dissolved drug.

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The Lai et al. reference describes a method for crosslinking porous materials made from biodegradable polymers (e.g., collagen, polysaccharides, synthetic polymers, see Col. 3, lines 38-43) by introducing a supercritical fluid containing a cross-linking agent into a chamber containing the polymer to effect crosslinking. The method optionally includes introducing a pure supercritical fluid into the chamber subsequent to crosslinking to remove unreacted cross-linking agent from the cross-linked polymer.

The Carli et al. reference describes a method for impregnating a cross-linked polymer with a drug using a supercritical fluid. The Carli et al. reference describes dissolving a drug in a supercritical fluid, contacting the drug containing fluid with a cross-linked polymer to impregnate the polymer with the drug, and then removing the supercritical fluid to provide a drug loaded cross-linked polymer.

Neither the Lai et al. nor Carli et al. references teach the step of contacting a cross-linked polymer with supercritical fluid free from any drug as a pre-treatment for drug loading. In contrast to the claimed invention, the Lai et al. reference describes delivering a cross-linking agent to a polymer to be cross-linked through the use of a supercritical fluid that includes a dissolved cross-linking agent. The Carli et al. reference describes delivering a drug to a polymer using a supercritical fluid, but fails to describe any pre-treatment of cross-linked polymer to be impregnated by a drug. The cited references fail to teach or even remotely suggest any process that includes pre-treating a cross-linked polymer with supercritical fluid free from any drug prior to loading that cross-linked polymer with a drug compound.

Despite the Examiner's reiteration of the previously set forth characterization of the cited references, applicants submit that neither of the cited references teaches or suggests the claimed process in which the first step requires treating a polymer with a supercritical fluid prior to contacting the pretreated polymer with a supercritical fluid containing a dissolved drug.

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Even assuming that the combined teachings of the cited references did teach each and every limitation of the claimed invention, which they do not, the prima facie case of obviousness appears to be premised on the motivation to combine the disparate teachings of the cited references. The Office Action states that the skilled person "would have found it obvious to combine these references since the method of drug loading was known at the time of the invention and Lai et al. explicitly teach the use of their materials to deliver drugs." Applicants respectfully submit that this statement does not rise to the required articulated reasoning with rational underpinning demonstrating an apparent reason to combine the known elements in the fashion claimed.

A proper case of prima facie obviousness must include motivation to combine the cited references. Obvious rejections cannot be sustained by mere conclusory statements. Rather, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. Unsupported assertions are not adequate. Applicants therefore respectfully traverse the rejection as there is no "apparent reason" to modify the references as suggested by the Examiner. See *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (there should be an "explicit" analysis regarding "whether there was ***an apparent reason*** to combine the known elements ***in the fashion claimed*** by the patent at issue.") (Emphasis added.) Applicants further submit that, in addition to there being no apparent reason to combine the references, the Examiner has failed to articulate one. Withdrawal of the rejection is respectfully requested.

As an initial matter, the Office Action does not indicate where either cited reference discloses a "pre-treatment step" of treating the cross-linked polymer with supercritical fluid free from any drugs before contacting the pre-treated polymer with the supercritical fluid containing

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the drug. Therefore, the Examiner failed to complete the required reasoning by disregarding the recited step of the claimed process.

Furthermore, the Examiner appears to have selected only those portions of the Lai reference that purportedly lead to the claimed invention. Applicants respectfully submit that the Examiner has not considered the teaching of the reference as a whole and, as such, has improperly engaged in hindsight analysis to reconstruct the claimed process.

Applicants submit that there is no motivation to combine the cited references as the Examiner has. Furthermore, applicants submit that the Examiner has failed to articulate the basis for the motivation. The mere statement that each of the cited references "teach the use of materials to deliver drugs" is not an articulation of an apparent reason to combine the elements.

The claimed invention provides unexpected results

Furthermore, the method of the invention, which includes a pre-treatment step, provides unexpected results with regard to drug loading and the subsequent bioavailability of the loaded drug.

As set forth in the application as originally filed and as described in detail in applicants' previous response filed July 29, 2008 (incorporated herein), applicants have surprisingly found that pre-treatment of a cross-linked polymer with pure supercritical fluid provides for a higher degree and more rapid kinetic of the drug loading into cross-linked polymers compared to processes that do not include a pre-treatment step.

The Examiner refers to the Berens and Domingo references to support the position that the evidence referred to by applicants to support non-obviousness is not commensurate in scope with the claimed process. Applicants respectfully disagree.

Examples 1-3 are comparative examples where, for each example, the identical features regarding drug/polymer/fluid are compared with or without the pre-treatment step. Therefore, in

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calculating the percentage of the drug loading in each example and in realizing that the loading percentage of the drug increases in the presence of the pre-treatment step, no relevance was given to the kind of polymer/drug/fluid, because these features were the same in each single evaluation. The pre-treatment step for the same polymer/drug/fluid influences the result of the drug loading percentage in the method.

Therefore, even if Berens et al. teach that the ability of the polymer to be infused by a drug/additive varies greatly depending upon the particular combination of drug/additive and polymer, this has no relevance because the increase of drug loading in the invention method is due to the pre-treatment step and not to a specific drug/polymer, which is the same in the method with the pre-treatment (invention) and without pre-treatment (prior art). The loading percentage increase in Examples 1-3 is ascribable to the pre-treatment step without changing drug/polymer or fluid of the method without pre-treatment.

The same is true for the temperature/pressure/time conditions. In Examples 1 and 2 the conditions of the treatment with supercritical fluid are the same with or without the pre-treatment and the increase of the drug loading was achieved in the method of the invention.

The Examiner refers to the Domingo et al. reference for the teaching that, for a given time period, a higher temperature and pressure result in a higher loading of a solute in a polymer via supercritical fluid treatment and, depending on the polymer and solute, a 10° difference in the temperature of the supercritical fluid could result in a 23% change in loading. The Examiner concludes that the 23% difference shown for Example 3 is not instructive or demonstrative as it initially seems and that, therefore, some processing conditions may not yield a different result when comparing the claimed method to methods that include no pre-treatment.

First, the Domingo reference relates to the absorption of a drug on alumina, silica gel, and polystyrene divinylbenzene which are not cross-linked polymers. Therefore, applicants question

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the relevancy of the reference to the claimed process. Furthermore, on page 155, the reference concludes by affirming that "increasing adsorption temperature from 318-353K, the increase in the total uptake was mainly reflected in the adsorption of benzoic acid, while the adsorption of salicylic acid remained constant . . . or . . . increased only slightly." Therefore, also having a difference of temperature of at least 35°C, because 318-353K corresponds to 44-80°C, the increase was not always proved. In view of Examples 1 and 2, it is clear that the pre-treatment step makes the difference for achieving a loading increase of 23%.

Conclusion

Not only do the cited references fail to teach or suggest any method that includes pre-treating a cross-linked polymer with a supercritical fluid for any purpose, but the claimed method provides unexpected advantageous results with regard to both increasing the amount of drug that can be loaded into the cross-linked polymer as well as increasing the bioavailability of the loaded drug.

Because the cited references fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed, the claimed invention is nonobvious and patentable over the cited references. Withdrawal of the rejection is requested.

The Rejection of Claims 10-14 Under 35 U.S.C.§103(a)

Claims 10-14 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,670,454, issued to Lai et al., in view of U.S. Patent No. 5,736,371, issued to Samain et al. Withdrawal of the rejection is requested for the following reasons.

Claim 10 is an independent claim directed to a method for increasing the drug-loading capacity of a cross-linked polymer that includes treating the cross-linked polymer (cross-linked cellulose, starch, and cross-linked cyclodextrins) with a supercritical fluid that does not contain any drugs. Claims 11-14 depend from Claim 10.

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The deficiencies of the teaching of the Lai reference described in detail above with regard to Claim 1 are not cured by the teaching of the Samain reference. The Samain reference describes a process for synthesizing a biodegradable particulate vector that includes the steps of preparing a matrix by crosslinking a biodegradable polysaccharide, reacting the matrix with a dicarboxylic acid monochloride to provide a vector nucleus, grinding the vector nucleus to reduce its size, chemically coupling a fatty acid compound to the vector nucleus to provide a first layer on the vector, and hydrophobically bonding amphiphilic compounds to the first layer to provide a second layer. The vector is described as useful for transporting molecules having biological activity. The Examiner appears to rely on this reference for using cross-linked cellulose and starch in a drug delivery device.

Because the cited references fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed, the claimed invention is nonobvious and patentable over the cited references. Withdrawal of the rejection is requested.

Rejoinder of Claims 16-21

Rejoinder of Claims 16-21 is requested. Claims 16-19 relate to a modified cross-linked polymer having enhanced drug-loading properties prepared by treating the cross-linked polymer with supercritical fluid free from any drug. Claim 20 relates to the modified cross-linked polymer of Claim 16 further including a drug. Claim 21 relates to a pharmaceutical composition containing the drug loaded modified cross-linked polymer of Claim 20. In view of the above amendments and foregoing remarks, rejoinder and allowance of Claims 16-21 is respectfully requested.

CONCLUSION

In view of the above amendments and foregoing remarks, applicants believe that Claims 1-14 and 16-21 are in condition for allowance. If any issues remain that may be

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expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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